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Terms	Documents
(inactivat\$ or disrupt\$ or non-function\$ or mutat\$) near7 (alpha adj 1 adj 3 adj (galactosyltransferase or gt))	3

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### Search History

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<i>DB=PGPB,USPT; PLUR=YES; OP=AND</i>			
<u>L4</u>	(inactivat\$ or disrupt\$ or non-function\$ or mutat\$) near7 (alpha adj 1 adj 3 adj (galactosyltransferase or gt))	3	<u>L4</u>
<u>L3</u>	11 and L2	1	<u>L3</u>
<u>L2</u>	porcine adj cell	437	<u>L2</u>
<u>L1</u>	(inactivat\$ or disrupt\$ or non-function\$ or mutat\$) near5 (alpha adj 1 adj 3 adj (galactosyltransferase or gt))	3	<u>L1</u>

END OF SEARCH HISTORY

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☐ 1. 6849448. 04 Dec 97; 01 Feb 05. Pigs and pig cells having an inactivated .alpha. 1,3-galactosyl transferase gene. D'Apice; Anthony J. F., et al. 435/325; 435/320.1 435/455 536/23.1 536/23.5. C12N005/00 C12N015/00 C12N015/63 C07H021/02 C07H021/04 .

☐ 2. 6361775. 15 Oct 98; 26 Mar 02. Compositions and methods for vaccines comprising .alpha.-galactosyl epitopes. Galili; Uri, et al. 424/184.1; 424/155.1 424/156.1 424/218.1 424/277.1 424/278.1 424/816 530/387.1. A61K039/00 A61K039/38 A61K039/12 A61K039/395 C07K016/00 .

☐ 3. 5879675. 11 Sep 96; 09 Mar 99. Compositions and methods for vaccines comprising .alpha.-galactosyl epitopes. Galili; Uri, et al. 424/93.1; 424/155.1 424/156.1 424/159.1 424/184.1 424/218.1 424/277.1 424/278.1 424/816. A61K039/395 A61K039/12 A61K045/00 A01N063/00 .

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Terms	Documents
(inactivat\$ or disrupt\$ or non-function\$ or mutat\$) near7 (alpha adj 1 adj 3 adj (galactosyltransferase or gt))	3

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(FILE 'HOME' ENTERED AT 18:38:54 ON 24 MAY 2006)

FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH, LIFESCI' ENTERED AT 18:39:15 ON 24 MAY 2006

L1 80 S (INACTIVAT? OR DISRUPT? OR NON-FUNCTION? OR MUTAT?) (5A) (ALPHA  
L2 43 DUP REM L1 (37 DUPLICATES REMOVED)  
L3 1433 S PORCINE(W)CELL  
L4 1 S L2 AND L3

=> d au ti so pi 20-43 l2

L2 ANSWER 20 OF 43 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on  
STN  
AU Koike, Chihiro [Reprint author]; Fung, John J.; Geller, David A.; Kannagi,  
Reiji; Libert, Therese; Luppi, Patrizia; Nakashima, Izumi; Profozich,  
Jennifer; Rudert, William; Sharma, Sugandha B.; Starzl, Thomas E.; Trucco,  
Massimo  
TI Molecular basis of evolutionary loss of the alpha1,3-galactosyltransferase  
gene in higher primates.  
SO Journal of Biological Chemistry, (March 22, 2002) Vol. 277, No. 12, pp.  
10114-10120. print.  
CODEN: JBCHA3. ISSN: 0021-9258.

L2 ANSWER 21 OF 43 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 8  
AU Dai, Yifan; Vaught, Todd D.; Boone, Jeremy; Chen, Shu-Hung; Phelps, Carol  
J.; Ball, Suyapa; Monahan, Jeff A.; Jobst, Peter M.; McCreath, Kenneth J.;  
Lamborn, Ashley E.; Cowell-Lucero, Jamie L.; Wells, Kevin D.; Colman,  
Alan; Polejaeva, Irina A.; Ayares, David L.  
TI Targeted **disruption** of the **.alpha.1,**  
**3-galactosyltransferase** gene in cloned pigs  
SO Nature Biotechnology (2002), 20(3), 251-255  
CODEN: NABIF9; ISSN: 1087-0156

L2 ANSWER 22 OF 43 CAPLUS COPYRIGHT 2006 ACS on STN  
AU Raeder, Roberta H.; Badylak, Stephen F.; Sheehan, Christine; Kallakury,  
Bhaskar; Metzger, Dennis W.  
TI Natural anti-galactose  $\alpha$ 1,3 galactose antibodies delay, but do not  
prevent the acceptance of extracellular matrix xenografts  
SO Transplant Immunology (2002), 10(1), 15-24  
CODEN: TRIME2; ISSN: 0966-3274

L2 ANSWER 23 OF 43 CAPLUS COPYRIGHT 2006 ACS on STN  
IN Denning, Chris; Clark, John  
TI Animal tissue for xenotransplantation  
SO PCT Int. Appl., 86 pp.  
CODEN: PIXXD2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001088096	A2	20011122	WO 2001-US15765	20010514
	WO 2001088096	A3	20030710		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	US 2005287581	A1	20051229	US 2005-198685	20050804

L2 ANSWER 24 OF 43 CAPLUS COPYRIGHT 2006 ACS on STN  
 IN Koike, Chihiro  
 TI Mammalian  $\alpha$ 1-3 galactosyltransferase genes and promoters and their  
 uses  
 SO PCT Int. Appl., 138 pp.  
 CODEN: PIXXD2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001030992	A2	20010503	WO 2000-US29139	20001020
WO 2001030992	A3	20020131		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2426669	AA	20010503	CA 2000-2426669	20001020
US 2003203427	A1	20031030	US 2002-125994	20020419

L2 ANSWER 25 OF 43 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 9  
 AU Xu, Hui; Shama, Ajay; Chen, Libing; Harrison, Caren; Wei, Yuanyuan; Chong,  
 Anita S.-F.; Logan, John S.; Byrne, Guerard W.  
 TI The structure of anti-Gal immunoglobulin genes in naive and stimulated Gal  
 knockout mice  
 SO Transplantation (2001), 72(11), 1817-1825  
 CODEN: TRPLAU; ISSN: 0041-1337

L2 ANSWER 26 OF 43 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 10  
 AU Nozawa, Satoshi; Xing, Pei-Xiang; Wu, Gordon D.; Gochi, Eiji;  
 Kearns-Jonker, Mary; Swensson, Joyce; Starnes, Vaughn A.; Sandrin, Mauro  
 S.; McKenzie, Ian F. C.; Cramer, Donald V.  
 TI Characteristics of immunoglobulin gene usage of the xenoantibody binding  
 to Gal- $\alpha$ (1,3)Gal target antigens in the Gal knockout mouse  
 SO Transplantation (2001), 72(1), 147-155  
 CODEN: TRPLAU; ISSN: 0041-1337

L2 ANSWER 27 OF 43 MEDLINE on STN DUPLICATE 11  
 AU Xing L; Xia G H; Fei J; Huang F; Guo L H  
 TI Adenovirus-mediated expression of pig  $\alpha$ 1, 3 galactosyltransferase  
 reconstructs Gal  $\alpha$ 1, 3 gal epitope on the surface of human tumor  
 cells.  
 SO Cell research, (2001 Jun) Vol. 11, No. 2, pp. 116-24.  
 Journal code: 9425763. ISSN: 1001-0602.

L2 ANSWER 28 OF 43 CAPLUS COPYRIGHT 2006 ACS on STN  
 AU Chong, A. S.-F.; Blinder, L.; Ma, L.; Yin, D.; Shen, J.; Williams, J. W.;  
 Byrne, G.; Schwarz, A.; Diamond, L. S.; Logan, J. E.  
 TI Anti-galactose- $\alpha$ (1,3)galactose antibody production in  
 $\alpha$ 1,3-galactosyltransferase gene knockout mice after xeno- and  
 allotransplantation  
 SO Transplantation Proceedings (2000), 32(5), 844-845  
 CODEN: TRPPA8; ISSN: 0041-1345

L2 ANSWER 29 OF 43 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 12  
 AU Tanemura, Masahiro; Maruyama, Shoichi; Galili, Uri  
 TI Differential expression of  $\alpha$ -gal epitopes (Gal $\alpha$ 1-3Gal $\beta$ 1-  
 4GlcNAc-R) on pig and mouse organs  
 SO Transplantation (2000), 69(1), 187-190  
 CODEN: TRPLAU; ISSN: 0041-1337

L2 ANSWER 30 OF 43 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 13  
AU Chong, Anita S.-F.; Blinder, Leonard; Ma, Lianli; Yin, Dengping; Shen, Jikun; Williams, James W.; Byrne, Gerry; Schwarz, Alex; Diamond, Lisa S.; Logan, John E.  
TI Anti-galactose- $\alpha$ (1,3) galactose antibody production in  $\alpha$ 1,3-galactosyltransferase gene knockout mice after xeno and allo transplantation  
SO Transplant Immunology (2000), 8(2), 129-137  
CODEN: TRIME2; ISSN: 0966-3274

L2 ANSWER 31 OF 43 CAPLUS COPYRIGHT 2006 ACS on STN  
AU Galili, Uri; Tanemura, Masahiro  
TI Significance of  $\alpha$ -Gal (Gal $\alpha$ 1-3Gal $\beta$ 1-4GlcNAc-R) epitopes and  $\alpha$ 1,3 galactosyltransferase in xenotransplantation  
SO Trends in Glycoscience and Glycotechnology (1999), 11(62), 317-327  
CODEN: TGGLEE; ISSN: 0915-7352

L2 ANSWER 32 OF 43 CAPLUS COPYRIGHT 2006 ACS on STN  
IN D'Apice, Anthony J. F.; Pearse, Martin J.; Robins, Allan J.; Crawford, Robert J.; Rathjen, Peter D.  
TI Minimizing hyperacute rejection in human xenotransplantation by elimination of antigenic polysaccharides  
SO U.S., 92 pp., Cont.-in-part of U.S. Ser. No. 188,607, abandoned.  
CODEN: USXXAM

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5849991	A	19981215	US 1995-378617	19950126
CA 2181433	AA	19950803	CA 1995-2181433	19950127
EP 755451	A1	19970129	EP 1995-907116	19950127
EP 755451	B1	20050525		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
BR 9506652	A	19970902	BR 1995-6652	19950127
AT 296349	E	20050615	AT 1995-907116	19950127
ES 2247588	T3	20060301	ES 1995-907116	19950127
US 6849448	B1	20050201	US 1997-984900	19971204
AU 9877428	A1	19981001	AU 1998-77428	19980721
AU 711144	B2	19991007		
US 2004171155	A1	20040902	US 2004-762888	20040121

L2 ANSWER 33 OF 43 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 14  
AU Vanhove, Bernard; Charreau, Beatrice; Cassard, Armelle; Pourcel, Christine; Soullillou, Jean-Paul  
TI Intracellular expression in pig cells of anti- $\alpha$ 1,3 galactosyltransferase single-chain Fv antibodies reduces Gal $\alpha$ 1,3Gal expression and inhibits cytotoxicity mediated by anti-Gal xenoantibodies  
SO Transplantation (1998), 66(11), 1477-1485  
CODEN: TRPLAU; ISSN: 0041-1337

L2 ANSWER 34 OF 43 LIFESCI COPYRIGHT 2006 CSA on STN  
AU d'Apice, A.J.F.; Pearse, M.J.; Robins, A.J.; Crawford, R.J.; Rathjen, P.D.  
TI Mice homozygous for an inactivated alpha 1,3-galactosyl transferase gene (19981215) . US Patent 5849991; US Class: 800/2; 800/DIG.1; 800/DIG.2; 435/172.3; 435/320.1; 435/354..  
SO (19981215) . US Patent 5849991; US Class: 800/2; 800/DIG.1; 800/DIG.2; 435/172.3; 435/320.1; 435/354..

L2 ANSWER 35 OF 43 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 15  
AU Shinkel, Trixie A.; Chen, Chao-Guang; Salvaris, Evelyn; Henion, Timothy R.; Barlow, Helen; Galili, Uri; Pearse, Martin J.; D'Apice, Anthony J. F.  
TI Changes in cell surface glycosylation in  $\alpha$ 1,3-galactosyltransferase knockout and  $\alpha$ 1,2-fucosyltransferase transgenic mice  
SO Transplantation (1997), 64(2), 197-204  
CODEN: TRPLAU; ISSN: 0041-1337

L2 ANSWER 36 OF 43 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on

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AU Soullillou J P (Reprint)  
TI Immunological problems specific to xenografts  
SO BIODRUGS, (1997) Vol. 8, Supp. [1], pp. 29-32.  
ISSN: 1173-8804.

L2 ANSWER 37 OF 43 MEDLINE on STN DUPLICATE 16  
AU Tearle R G; Tange M J; Zannettino Z L; Katerelos M; Shinkel T A; Van  
Denderen B J; Lonie A J; Lyons I; Nottle M B; Cox T; Becker C; Peura A M;  
Wigley P L; Crawford R J; Robins A J; Pearse M J; d'Apice A J  
TI The alpha-1,3-galactosyltransferase knockout mouse. Implications for  
xenotransplantation.  
SO Transplantation, (1996 Jan 15) Vol. 61, No. 1, pp. 13-9.  
Journal code: 0132144. ISSN: 0041-1337.

L2 ANSWER 38 OF 43 CAPLUS COPYRIGHT 2006 ACS on STN  
IN Baetscher, Manfred W.; Sachs, David H.; Gustafsson, Kenth T.  
TI  $\alpha(1,3)$ -galactosyltransferase negative swine and use for prevention  
of xenogenic transplant rejection  
SO PCT Int. Appl., 58 pp.  
CODEN: PIXXD2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9528412	A1	19951026	WO 1995-US3940	19950331
	W: AU, CA, JP, KR, MX, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2187802	AA	19951026	CA 1995-2187802	19950331
	AU 9522332	A1	19951110	AU 1995-22332	19950331
	EP 755402	A1	19970129	EP 1995-915459	19950331
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	JP 10504442	T2	19980506	JP 1995-526984	19950331
	US 6153428	A	20001128	US 1996-621700	19960326
	US 6413769	B1	20020702	US 1997-929940	19970915
	AU 9918505	A1	19990429	AU 1999-18505	19990301
	AU 766519	B2	20031016	AU 2001-79336	20011010
	US 2003014770	A1	20030116	US 2002-98276	20020315
	AU 2004200177	A1	20040212	AU 2004-200177	20040116

L2 ANSWER 39 OF 43 CAPLUS COPYRIGHT 2006 ACS on STN  
IN Pearse, Martin J.; Crawford, Robert J.; Robbins, Allan J.; Rathjen, Peter  
D.; d'Apice, Anthony J. F.  
TI Minimizing hyperacute rejection in human xenotransplantation by  
elimination of xenoantibodies and of antigenic polysaccharides  
SO PCT Int. Appl., 183 pp.  
CODEN: PIXXD2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9520661	A1	19950803	WO 1995-IB88	19950127
	W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9515445	A1	19950815	AU 1995-15445	19950127
	AU 695373	B2	19980813		
	EP 755451	A1	19970129	EP 1995-907116	19950127
	EP 755451	B1	20050525		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	JP 09508277	T2	19970826	JP 1995-519965	19950127
	BR 9506652	A	19970902	BR 1995-6652	19950127
	AT 296349	E	20050615	AT 1995-907116	19950127

L2 ANSWER 40 OF 43 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on  
STN

AU Galili, Uri [Reprint author]; Andrews, Peter  
 TI Suppression of alpha-galactosyl epitopes synthesis and production of the natural anti-Gal antibody: A major evolutionary event in ancestral Old World primates.  
 SO Journal of Human Evolution, (1995) Vol. 29, No. 5, pp. 433-442. CODEN: JHEVAT. ISSN: 0047-2484.

L2 ANSWER 41 OF 43 LIFESCI COPYRIGHT 2006 CSA on STN  
 AU Galili, U.; Gregory, C.R.; Morris, R.E.  
 TI Contribution of anti-Gal to primate and human IgG binding to porcine endothelial cells  
 SO TRANSPLANTATION, (1995) vol. 60, no. 2, pp. 210-212. ISSN: 0041-1337.

L2 ANSWER 42 OF 43 CAPLUS COPYRIGHT 2006 ACS on STN  
 AU Henion, Timothy R.; Macher, Bruce A.; Anaraki, Farvardin; Galili, Uri  
 TI Defining the minimal size of catalytically active primate  $\alpha$ 1,3 galactosyltransferase: structure-function studies on the recombinant truncated enzyme  
 SO Glycobiology (1994), 4(2), 193-201 CODEN: GLYCE3; ISSN: 0959-6658

L2 ANSWER 43 OF 43 MEDLINE on STN DUPLICATE 17  
 AU Galili U; Swanson K  
 TI Gene sequences suggest **inactivation of alpha-1,3-galactosyltransferase** in catarrhines after the divergence of apes from monkeys.  
 SO Proceedings of the National Academy of Sciences of the United States of America, (1991 Aug 15) Vol. 88, No. 16, pp. 7401-4. Journal code: 7505876. ISSN: 0027-8424.

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L4 ANSWER 1 OF 1 LIFESCI COPYRIGHT 2006 CSA on STN  
 AN 95:105699 LIFESCI  
 TI Contribution of anti-Gal to primate and human IgG binding to porcine endothelial cells  
 AU Galili, U.; Gregory, C.R.; Morris, R.E.  
 CS Dep. Microbiol. and Immunol., Med. Coll. Pennsylvania, Philadelphia, PA, USA  
 SO TRANSPLANTATION, (1995) vol. 60, no. 2, pp. 210-212. ISSN: 0041-1337.  
 DT Journal  
 FS F  
 LA English  
 AB Hyperacute rejection of porcine organs transplanted into primates is mediated by natural preexisting IgM antibodies that bind to porcine endothelial cells (PEC) lining the porcine blood vessels, fix complement, and thus cause the lysis of these cells. A number of recent studies have suggested that a large proportion of these lytic antibodies display anti-Gal specificity. Anti-Gal is a natural antibody that constitutes approximately 1% of circulating immunoglobulins in Old World monkeys (monkeys of Asia and Africa), apes, and humans and can be produced by as many as 1% of B lymphocytes. It interacts specifically with the carbohydrate structure Gal alpha 1-3Gal beta 1-4GlcNAc-R (termed the alpha -galactosyl epitope), which is expressed as several millions of epitopes per cell in nonprimate mammals (including PEC) and New World monkeys (i.e., monkeys of South and Central America). The alpha -galactosyl epitope is absent from Old World monkeys, apes, and humans. This is since the gene for the glycosylation enzyme that synthesizes the alpha -galactosyl epitope (i.e., **alpha 1,3 galactosyltransferase**) was **inactivated** in ancestral Old World primates. Recent studies have indicated that hyperacute rejection of

porcine xenografts in primates could be prevented by inactivation of complement in the primate serum or by the expression of human decay accelerating factor or CD59 on the PEC of transgenic pigs used as the organ donors. In the absence of complement-mediated lysis, chronic destruction of porcine xenograft cells may be mediated by IgG antibodies binding to these cells and directing various killer cells (e.g., granulocytes and monocytes/macrophage) to bind to the antibody coated PEC via their Fc receptors, and exert the cytotoxic potential by the antibody-dependent cell cytotoxicity (ADCC) mechanism. Anti-Gal IgG isolated from normal human serum was indeed found to effectively mediate the destruction of **porcine cells**-including endothelial cells, smooth muscle cells, and fibroblasts-by ADCC. Since anti-Gal IgM antibody was found to be the main antibody-mediating complement-induced lysis of PEC, it was of interest to determine if anti-Gal is also the predominant serum IgG antibody that binds to live PEC, or whether there is a significant moiety of other natural IgG antibodies that interact with PEC. In order to simulate the interaction of IgG molecules with PEC lining blood vessels, the antibody binding was assessed with confluent monolayers of live PEC grown in 60-mm culture dishes (rather than with PEC in suspension or fixed PEC), and subsequently with super(125)I protein-A, which interacts specifically with the Fc portion of IgG molecules. The possible occurrence of IgG anti-PEC antibodies that are not anti-Gal was assessed by comparing anti-PEC activity in the serum of primates that lack anti-Gal-i.e., New World monkeys-with that in Old World monkeys, or human serum. In addition, the anti-PEC IgG antibody activity was determined in Old World monkey and human serum after the specific removal of anti-Gal from the serum by adsorption. Dog sera, which contain anti-PEC antibodies, but lack anti-Gal because of synthesis of autologous alpha -galactosyl epitopes, were used as control.

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